The APOE paradox: how do attentional control differences in mid-adulthood reflect risk of late-life cognitive decline

Article (Accepted Version)

The *APOE* paradox: how do attentional control differences in mid-adulthood reflect risk of late-life cognitive decline.

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Acceptance date: 18/08/16

Abstract

Possession of an *APOE* e4 allele is an established risk factor for Alzheimer's disease, while the less commonly studied e2 variant is premised to offer some protection. This research explores the purported deleterious-protective dichotomy of *APOE* variants on attentional control in mid-adulthood. 66 volunteers, aged 45-55 years, completed three tasks that provided complementary measures of attentional control: prospective memory, sustained attention and inhibition. Performance was compared between e2 carriers, e4 carriers and e3 homozygotes (the population norm). Carriers of the e4 allele showed subtle disadvantages, compared to the e3 group, in accuracy of Stroop task and prospective memory performance. Contrary to expectations, e2 carriers showed performance disadvantages in sustained attention. The finding of detrimental effects in attentional control for both e4 and e2 complicates the current model that proposes opposing effects of these variants on later-life cognition. Future research is needed to understand how cognitive differences develop with increasing age, and the physiological mechanisms that underpin these changes.

Keywords: *APOE,* Cognitive Ageing, Alzheimer's disease, Attention, Executive Function, Mid-adulthood

1. Introduction

Cognitive ageing is differentially associated with the three variants (e2, e3, and e4) of the Apolipoprotein E (*APOE*) gene, a single nucleotide polymorphism. The e4 allele, present in approximately 25% of the population, is associated with increased risk of Alzheimer's disease (AD) (Corder et al., 1993). While the e3 allele is positioned as the population norm, possession of an e2 allele, prevalent in ~15% of the population (Raber et al., 2004) is hypothesised to be protective against AD risk (e.g. Farrer et al., 1997; Lippa et al., 1997; Wilson et al., 2002).

In addition, carrying at least one copy of the *APOE* e4 allele has been associated with poorer cognition in healthy older adults, with effects most commonly reported in episodic memory (e.g Caselli et al., 1999; O' Hara et al., 1998; Staehelin et al., 1999; Packard et al., 2007), but not isolated to this domain (e.g. Berteau-Pavy et al., 2007; Reinvang et al., 2010; Small et al., 2004; Wisdom et al., 2011). Not all studies have been consistent in reporting an effect of *APOE* e4 in older adulthood, however (e.g. Bunce et al., 2014; Bunce et al., 2004; Juva et al., 2000; Kim et al., 2002; Salo et al., 2001).

Significantly, effects of carrying an *APOE* e4 allele are not isolated to ageing populations, with reports of subtle cognitive differences in e4 carriers from childhood (Acevedo et al., 2010; Bloss et al., 2008). Evidence for cognitive advantages in young e4 carriers has been reported within the domains of episodic memory, executive function (EF) and attention (Marchant et al., 2010; Mondadori et al., 2007; Rusted et al., 2013; Taylor et al., 2016), contrasting with the detrimental associations of *APOE* e4 in later adulthood. As effects of e4 are detectable in youth, however, this highlights the need to consider *APOE* genotype earlier in the ageing trajectory.

The cognitive effects of *APOE* in mid-adulthood are of crucial interest as this may be when the e4 allele is first exerting detrimental effects on the ageing trajectory. To date, reported effects of *APOE* e4 in mid-adulthood are inconsistent (for review; Lancaster et al., under review; Rusted & Carare, 2015; Salvato, 2015), with many studies reporting null effects. The exceptions are studies within the domain of memory, where detrimental effects are reported from the end of the fifth decade (Caselli et al., 2004; Jochemsen et al., 2012; Schultz et al., 2008). The inconsistency of reported findings is likely to stem from several methodological issues, including variation in age group included, control of potential moderators and sensitivity of cognitive tasks used. Moreover, as the effect of *APOE* e4 is non-uniform across cognition, the domain under study represents another factor in the inconsistency.

Aside from memory, attentional control, necessary to complete any goal-driven behaviour, may show sensitivity to *APOE* status in mid-adulthood. Both attentional control mechanisms and EF deficits have been associated with the preclinical stages of dementia (Carlson et al., 2009; Harrington et al., 2013; Twamley et al., 2006). Frontal regions, the predominant neural focus of executive attention, are vulnerable early in the ageing trajectory to both a loss of neural integrity and the deposition of amyloid, with this pattern reported in both healthy and pathological ageing (Bartzokis et al., 2003; Raz, 2000; Rowe et al., 2007; Villemagne et al., 2011). Further supporting the sensitivity of attentional control to ageing processes, amongst a

battery of neuropsychological measures, the profile of errors and response time (RT) on a computerized Stroop-switch paradigm, an established measure of attentional selection and distractor inhibition, was found to best distinguish the cognitive profile of mild AD (Hutchison et al., 2010). In addition, performance on this task predicted the subsequent development of AD in a sample of older adults (Balota et al., 2010).

Neuropsychological assessments have not consistently found an effect of *APOE* e4 on attention or EF in mid-adulthood (Flory et al., 2000; Jochemsen et al., 2012; Sager et al., 2005), although genotype differences have been found using computerized research paradigms developed for maximum sensitivity. On a measure of sustained attention, e4 carriers (aged 45-55 years) demonstrated greater accuracy for detecting target strings, but slower RTs relative to a homozygous e3 group (Evans et al, 2014). This pattern of performance was replicated on a prospective memory (PM) measure in the same cohort, with e4 carriers demonstrating more accurate retrieval of PM intentions, but slower RTs on the ongoing task. Imaging data collected during the PM task found that in e4 carriers only, left inferior frontal gyrus activity correlated with retrieval accuracy. This was interpreted as evidence of a compensatory response within top-down attentional control mechanisms.

Failure to account for the effect of *APOE* e2 is likely a key factor in the reported inconsistency of *APOE*-related cognitive change in the literature to date. Predominantly, research either excludes e2 carriers, or considers e2 and e3 variants collectively as a non-e4 group, despite purported protective effects. In light of the opposing effects of *APOE* variants on dementia risk, intuitively differences are expected in the cognitive profile of e4 and e2 carriers. Recent research, however, has found overlapping patterns of task-related functional activity in mid-age e2 and e4 carriers, compared to an e3 group, during both a Stroop task, and an episodic memory task (Trachtenberg et al., 2012a). Both genotype groups also showed differences in resting-state activity compared to an e3 group (Trachtenberg et al., 2012b). This calls into question how the assumed dichotomy in *APOE* associated cognitive ageing manifests, and highlights *APOE* e2 as a crucial area for future research.

The current study provided a detailed investigation into the association between *APOE* and attentional control in mid-adulthood. The study aimed to extend previous findings of genotype differences within this domain (Evans at al., 2014) by administering a broader range of attentional tasks, allowing for a more in-depth exploration of the specific cognitive processes showing genotype sensitivity. The research also provided novel investigation into the hypothesised 'protective' e2 allele.

The behavioural session administered a rapid visual information processing task (RVIP; Wesnes & Warburton, 1983) and a PM measure (Rusted & Trawley, 2006), to establish if a speed-accuracy trade-off in e4 carriers is reliably observed. Specifically, the research expected to replicate the e4 advantage in PM retrieval, and target detection on the RVIP, in comparison to the population norm (e3 homozygotes), at the cost of response latency in this group. The processes targeted by these tasks include goal maintenance, switching, monitoring and updating, all of which burden executive attention and load on frontal lobes (Cona et al., 2015; Coull et al., 1996).
In addition, a computerized Stroop-switch task (Hutchison et al., 2010) was used to explore if errors on this task differentiate carriers of a genetic risk for AD as early as mid-adulthood. As

this task has previously been shown to distinguish older adults at heightened risk of developing Alzheimer's disease (Balota et al., 2010), by mid-age e4 carriers may show similar costs of incongruency on the proportion of errors made. Differences in task accuracy are linked to the ability to hold relevant information at the forefront of attention, and resist interference.

Despite reported protective effects of carrying an *APOE* e2 allele on longevity (Blanché et al., 2001; Frisoni et al., 2001) and cognition in older adulthood (Helkala et al., 1996; Wilson et al., 2002), understanding of how this variant affects cognition is limited at present. In light of recent research (Trachtenberg et al., 2012a; Trachtenberg et al., 2012b), it is unclear whether e2 carriers will show equal or advantaged performance compared to homozygous e3 carriers. This study took an exploratory look at the e2 effects on attentional control mechanisms, to provide the foundation for future work establishing the profile of this genotype in mid-adulthood.

Furthermore, the study addresses many of the methodological shortcomings within existing mid-age literature. The tasks record trial-by-trial response time data, as well as accuracy, to allow detailed analysis of performance on task. Additionally, the study recruits individuals from a narrow range of the lifespan (aged 45-55 years), and measures participant variables including education and cardiovascular health, which may moderate the influence of *APOE* on cognition.

2. Methods

2.1 Participants

165 healthy volunteers were recruited for the initial screening phase of this study, through advertisement at local universities, clubs, and community centers. For inclusion, volunteers were required to be aged 45-55 years, a non-smoker and using English as their daily-language. Exclusion criteria consisted of: a history of vascular health problems, untreated high blood pressure, psychoactive medication use, or a history of neurological trauma or psychiatric condition within the past 5 years.

The initial screening phase followed Human Tissue Authority (HTA) procedures, and the research ethics committee of the school of Psychology and Life Sciences, University of Sussex approved the full study. In line with ethical guidelines, volunteers first provided written informed consent, including acknowledgment that the results of the genotype analysis would not be made available to them. DNA was collected with a buccal swab, using an Isohelix SK1 kit. Genotyping followed triangulated anonymisation procedures, with two anonymised codes used per sample. Samples were analysed to determine *APOE* gene variant by LGC Genomics (Hertfordshire, www.lgcgroup.com/genomics). A fluorescence-based competitive allele-specific polymerase chain reaction determined the presence of three major *APOE* alleles (e2, e3, and e4) based on two *APOE* single nucleotide polymorphisms (SNPs) (rs429358, rd7412).

66 volunteers were invited to complete the behavioural session. Selection was made pseudo-randomly, in that efforts were made to ensure an approximately even numbers of participants in each genotype group (e2, e3, e4). Double-blind procedures were followed in that both the experimenter and participants remained blind to genotype. Distribution within genotype groups was as follows: 16 e2 carriers (2 e2/e2, 14 e2/e3), 26 e3 homozygotes, and 24 e4 carriers (17 e3/e4, 7 e4/e4). Volunteer characteristics are shown in Table 1.

2.2 Materials

2.2.1 Demographics and Baseline Cognitive Measures

A shortened version of the Nuffield Medical History Questionnaire assessed general state of health, recent medical history, medication use, and alcohol consumption. Additionally, the National Adult Reading Test (NART) (Nelson & Willison, 1991), a backward digit-span task and a visual simple response time task (SRT) were administered to provide baseline cognitive characteristics. For the SRT, participants were required to make a keyboard response ('space bar') as quickly as possible when presented with a visual target stimulus. The task consisted of 48 trials, with a mask of varying length (300ms-1000ms) present between each target stimulus. RTs greater or less than 3 standard deviation (SD) from a participant's mean RT were removed prior to analysis.

2.2.2 RVIP task

The RVIP task (Wesnes & Warburton, 1983) was administered for 4 minutes. A continuous stream of digits was presented to participants at a rate of 80 per minute, centrally on a computer monitor. Participants were required to monitor the digits, and respond when either 3 odd or 3 even digits appeared consecutively. Per each minute of the task, there were 8 target strings. Correct detections were recorded up to 1500ms after presentation of the third digit in the target string. Measures of response accuracy, response latency and number of false alarms (FA) (pressing when no target occurred) were recorded. Responses greater or less than 3 SD from each participant's mean RT were removed prior to analysis.

2.2.3 Card-sort PM task

The card-sort task (Rusted & Trawley, 2006) required participants to respond to a succession of playing card stimuli, displayed in a pseudo-random order on screen. In each trial, a card back was displayed for a variable duration (100-1000ms), followed by a card face, which was displayed for 1000ms. The on-going component of the task required participants to sort cards according to suit, pressing '1' for a spade and '3' for a hearts, as quickly and accurately as possible. Participants were asked to give no response if presented with a diamond or a club. Participants initially sorted one deck of 52 cards (26 sort trials, 26 non-sort trials) to provide a baseline measure of decision-making performance. Participants then received the PM instruction to press 'space' in response to the presentation of a specific target card, which was any card with the number '7'. Participants were asked to repeat this instruction back to the

experimenter in their own words to check understanding. They then completed 2 further decks of the on-going task with the additional PM instruction, containing 48 sort trials, 48 non-sort trials, and 8 PM trials.

Sort accuracy and RT was recorded for the baseline deck, and the 2 decks following the introduction of the PM instruction. For each volunteer, RTs more than 3 SD from their own mean were removed. Comparison of performance between these 2 conditions provides a measure of the cost of carrying a PM intention on ongoing sort performance. Accuracy of PM retrieval was also recorded.

2.2.4 Stroop-switch task

A computerised version of the Stroop-switch task was administered (Hutchison et al., 2010). Stimuli were presented on a black background and consisted of 4 colour words (blue, green, red and yellow) and 4 neutral words (bad, deep, legal, and poor) written in either blue, green, red or yellow font. Participants were required either to name the font colour or to read the word aloud. The naming rule (colour, word) switched throughout the task after every 2 trials. Trials were classified as either neutral (40 trials), when a neutral word appeared in any of the 4 font colours or incongruent (48 trials), when a colour word appeared in a non-matching font colour.

Participants completed 24 practice trials and 88 experimental trials. For each trial, a precue of 'word' or 'colour' in white font was presented for 1500ms, followed by a wait of 200ms, followed by the stimuli. Participants made a verbal response, with latency recorded using a microphone-connected serial response box. Stimuli remained on screen until a response was detected or 8000ms had elapsed. Accuracy of response was coded by the experimenter for each trial as correct, self-corrected error (e.g. 'bl..green') or intrusion error (i.e. if the participant says incongruent response). For each volunteer, only RTs for correct trials, and within 3 SD of their personal mean were considered for analysis.

2.3 Procedure

Volunteers selected from the screening phase took part in a single study session lasting 90 minutes. First, demographic and health measures including age, family history of dementia, height, weight, and blood pressure were collected. A measure of systolic and diastolic blood pressure was collected whilst seated, using an automatic arm-cuff machine on the right arm. Participants then completed a selection of experimental tasks and questionnaires in a fixed order (see Figure 1).

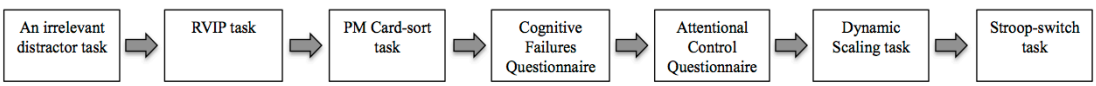

Figure 1. A timeline of the experimental tasks included in the behavioural session. The results of several experimental tasks administered in the session fell outside the scope of this paper and will be reported separately.

2.4 Design

Differences in the demographic and health characteristics of the genotype groups (e2, e3, e4) were analysed using a series of one-way analysis of variances (ANOVAs) for continuous variables, and chi-squared tests for categorical measures (gender, family history).

Across experimental tasks, analyses were first run to compare performance across all 3 genotype groups. All analyses were two-tailed. Gender was also included in parametric analyses to explore possible *APOE* X Gender interactions: as no interactions were found the effect of gender is not reported in the main body of results (main effects of gender are included as footnotes). For non-parametric analyses, data was screened for any differences by gender.

Secondary analyses were run selectively comparing e2 carriers and e4 carriers independently to the population norm (homozygous e3 carriers) where a main effect of genotype or genotype interaction term were significant or at trend level, or where specific predictions were made based on previous findings. The decision to run these secondary analyses were based on recent suggestions of similarity in the profile of e2 and e4 carriers, so separately comparing both groups to the population norm is needed for more detailed exploration.

2.4.1 Card-sort task

All volunteers retrieved at least 1 PM intention, taken as an indication that they had encoded and retained the PM intention, and so no volunteers were excluded from the analysis. Sort accuracy and RTs for correct sort responses were analysed, as well as accuracy of PM retrieval. A one-way ANOVA was used to assess group differences in baseline sort RT and accuracy, followed up by Bonferroni corrected independent *t*-tests to assess pair-wise genotype differences. A mixed ANOVA was conducted with deck (baseline, PM) as the within-subjects factor, and genotype group as the between-subjects factor, for both sort RT and accuracy, to assess performance change following introduction of the PM intention. Non-parametric tests were used to assess genotype differences in PM retrieval as the data violated assumptions of normality. A Kruskal-Wallis analysis was used to assess differences between all 3 genotype groups, followed by two separate Mann-Whitney U tests to compare both e4 and e2 variants to the e3 group, with a conservative alpha (α=. 025) applied.

2.4.2 RVIP

Number of target hits, hit latency, and number of FAs were analysed using separate ANOVAs, with time on task as the within-groups factor (time bins: minute 1-4) and genotype group (e2, e3, e4) as the between-groups factor. Separate analyses for both e2 and e4 were then completed to explore any suggested genotype effects.

2.4.3 Stroop-switch task

The distribution of RTs for Stroop-switch trials deviated from normality and hence a log transformation was applied to this variable prior to analysis. Initially, data was checked to search for an effect of rule switching (switch prior to trial, no switch prior to trial) on RTs and errors. There was no significant effect of switching, and switching did not interact with stimuli type, congruency or genotype (p>.05), and so these trials were considered collectively. For both RTs (correct trials) and proportion of errors, a mixed ANOVA was run with rule (colour, word) and congruency (incongruent, neutral) as the within-subjects factors, and genotype (e2, e3, e4) as the between-subject factor. Where present, interactions were probed with Bonferroni corrected t-tests. Separate analyses were then run comparing e2 and e4 variants to the e3 population norm to further explore suggested genotype effects.

3. Results

3.1 Demographics & Baseline Cognitive Measures

There were no significant genotype differences across the demographic measures (p>.05). Furthermore, no group differences were found in working memory (WM) span, or SRT (p>.05).

Table 1. *Demographics and baseline cognitive performance presented by genotype group.*

	Genotype Group		
Measure	**e2**	**e3**	**e4**
n	16	26	24
Age	50.44 (3.58)	49.04 (2.68)	49.17 (3.07)
Gender (% female)	75	73	63
Family History (%Yes)	25	35	54
Education	17.22 (3.24)	17.23 (3.13)	17.85 (4.32)
NART	119.06 (2.84)	118.56 (2.93)	116.87 (4.62)
BMI	24.02 (3.44)	26.24 (4.37)	25.15 (3.78)
Systolic BP	115.63 (7.55)	118.23 (8.47)	115.00 (8.76)
Diastolic BP	77.31 (9.99)	81.77 (10.63)	79.13 (7.77)
SRT (ms)	272 (44)	265 (32)	266 (27)
Digit-span	4.31 (1.30)	4.19 (1.50)	4.00 (1.65)

Note: Mean (sd)

3.2 Card-sort task

3.2.1. Baseline decision-making

Across participants, accuracy on the control 'decision-making' deck was at ceiling, with scores ranging from 50-52 correct (M=51.65) out of a maximum score of 52, with no significant difference between groups (p>.05). The genotype difference in decision-making RT approached significance, $F(2, 62)=2.92$, p=.061, n^2_p=.086. The e2 group trended towards

being slower than the e3 comparison group (p=.072), whereas the e4 and e3 groups did not differ in RT (p>.05).

3.2.2. PM performance

Introducing the PM intention was associated with a significant slowing of RTs on card-sort trials, $F(1, 62)=107.77$, $p<.001$, $n^2_p=.635$. The main effect of genotype and the interaction between deck and genotype group were non-significant, (p>.05). For sort accuracy, again introducing the PM intention was associated with a significant drop in accuracy, $F(1,62)=37.94$, $p<.001$, $n^2_p=.380$. The effect of genotype and the interaction between genotype and deck were both non-significant, (p>.05).

Across the 3 genotype groups there was no significant difference in retrieval of the PM targets (p>.05), although secondary analyses indicated e4 carriers (M=6.75, mean rank=21.46) retrieved fewer PM intentions than the e3 group (M=7.31; mean rank=29.23), and this difference approached significance, U=215, p=.040. There was no significant difference in the PM retrieval accuracy of e2 carriers (M=7.13, mean rank=20.62) compared to the e3 group (mean rank=22.04), U=222, p>.05.

Table 2. *Performance on the Card-sort task displayed by genotype group*.

Genotype	**Control deck**		**PM decks**		
	RT (ms)	**Accuracy/52**	**RT (ms)±sd**	**Accuracy/96**	**PM retrieval/8**
e2	606 ± 67	51.8	736 ± 64	93.00	7.13
e3	560 ± 77	51.5	710 ± 85	92.35	7.31
e4	590 ± 38	51.7	710 ± 69	93.13	6.75

3.3 RVIP

The data of 4 volunteers was removed prior to analysis due to comparable levels of hits and FAs, or a FA rate greater than 2 sd above the norm. For a summary of performance on this task by genotype group see Table 3.

Table 3. Overall performance on RVIP task by genotype, sd shown in brackets.

Genotype	**Mean hit detection/ 32**	**Mean hit latency (ms)**	**Mean false alarms**
e2	19.29 (6.28)	558 (69)	1.14 (1.41)
e3	23.52 (4.88)	510 (72)	2.09 (0.42)
e4	21.18 (7.20)	514 (77)	1.65 (0.35)

3.3.1 Hits

Accuracy decreased with time on task, $F(3, 171)=5.09$, p=.002, $n^2_p=.082$. Both the main effect of genotype, $F(2, 57)=2.72$, p=.087, $n^2_p=.087$, and the Time on task x Genotype interaction approached significance for number of hits, $F(6, 171)=5.09$, p=.074, $n^2_p=.064$.[1]

[1] The effect of gender on RVIP hit performance approached significance, $F(1, 57)=3.71$, p=.059, $n^2_p=.061$: males (mean=23.68) made more correct hits than females (mean=20.81).

Secondary analysis found the effect of genotype was driven by e2 carriers making significantly less hits than the e3 group, $F(1, 36)=5.51$, $p=.024$, $n^2_p=.133$. There was no significant difference between e4 carriers and e3 carriers ($p>.05$).

Further probing of the Time x Genotype interaction found e2 carriers made fewer hits than the e3 group only in minute 1, and this difference approached significance, t (17.7)=-2.72, $p=.014$. E4 carriers did not significantly differ from e3 carriers at any minute of the task.

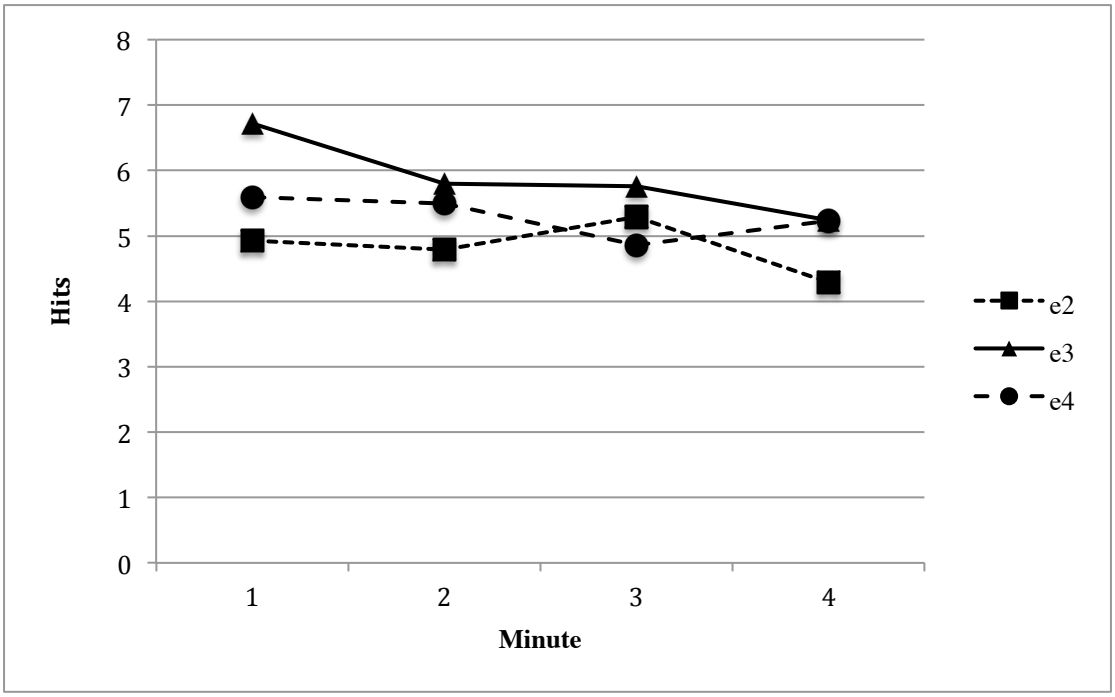

Figure 2. The Genotype x Time on task interaction for RVIP hit performance.

3.3.2 Hit Latency

With all 3 genotype groups included in the model, the effect of time on task on hit latency was non-significant ($p>.05$). The main effect of genotype and the Genotype x Time interaction were both non-significant ($p>.05$).

3.3.3 False Alarms

Both the main effects of time on task and genotype, and the interaction between Time x Genotype were non-significant ($p>.05$).

3.4 Stroop

3.4.1. Overall task performance

3.4.1.1 RTs

RTs were significantly slower for colour naming than word naming, $F(1, 60)=11.10$, $p=.001$, $n^2_p=.156$. Incongruency also led to significantly slower naming, $F(1, 60)=34.65$, $p<.001$,

n^2_p=.366, and this effect was larger for colour naming than word naming, $F(1, 60)=7.78$, p=.007, n^2_p=.115.[2]

3.4.1.2 Errors

There was no significant difference in the number of errors made for colour vs. word stimuli (p>.05). At trend level, more errors were made for incongruent stimuli than neutral stimuli, $F(1, 60)=3.10$, p=.089, n^2_p=.049. Again, there was a significant Rule x Congruency interaction, $F(1, 60)=12.17$, p=.001, n^2_p=.169. More errors were made for incongruent colour naming trials (M=.067) than neutral colour naming (M=.018), $t(63)=5.13$, p<.001. For word naming, more errors were made for neutral trials (M=.038) than incongruent trials (M=.017), $t(63)=-2.98$, p=.004 (Bonferroni corrected α=.013). [3]

3.4.2 Genotype effects

3.4.2.1 RTs

There were no genotype differences in RT (p>.05), and genotype status did not interact with either rule or congruency in affecting RT (p>.05).

3.4.2.1 Errors

The effect of genotype was non-significant (p >.05), as was the Congruency x Genotype interaction, $F(2, 60)=2.32$, p=.107, n^2_p=.072. The Genotype x Rule interaction, and the 3-way Genotype x Rule x Congruency interaction were both non-significant (p>.05).

The Congruency x Genotype interaction was probed in secondary analysis comparing e2 and e4 groups to the homozygous e3 group in separate models due to an a priori hypotheses of a genotype difference. There was no significant difference in the overall number of errors between the e3 group and e4 carriers (p>.05), but there was a significant Genotype x Congruency interaction, $F(1, 46)=4.27$, p=.044, n^2_p=.085, further explored with Bonferroni corrected t-tests (α =.013). There was no significant difference between errors on incongruent stimuli (M=.038) and neutral stimuli (M=.037) for e3 carriers (p>.0125), but e4 carriers made significantly more errors for incongruent (M=.052) than neutral stimuli (M=.022), $t(22)=2.73$, p=.012. There was no significant difference between e4 carriers and the e3 group in the proportion of errors made for neutral trials, or incongruent trials (p>.0125).

e2 carriers did not significantly differ from the e3 groups in the number of errors made (p>.05), and the Genotype x Congruency interaction was non-significant (p>.05). Additionally, e2 carriers did not show a significant cost of congruency on number of errors made (p>.05).

Table 4. Mean naming RT and the proportion of errors recorded, shown by condition and genotype for performance on the computerized Stroop task.

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[2] A main effect of gender on Stroop RTs was found with males slower in all trials, $F(1, 60)=5.90$, p=.029, n^2_p=.077. The effect of gender was more pronounced for trials with the rule 'word', than trials with the rule 'colour', $F(1, 60)=5.79$, p=.019, n^2_p=.088.

[3] There was a significant effect of gender on the proportion of errors made on the Stroop task, $F(1, 60)=9.64$, p=.003, n^2_p=.138, with males consistently making more errors.

			Genotype		
Stimuli	**Congruency**		**e2**	**e3**	**e4**
Colour					
	Neutral	RT (ms)	729 (126)	669 (123)	708 (107)
		Errors	.01	.02	.02
	Incongruent	RT (ms)	815 (131)	800 (177)	818 (128)
		Errors	.06	.06	.08
Word					
	Neutral	RT (ms)	683 (130)	623 (144)	662 (135)
		Errors	.03	.05	.03
	Incongruent	RT (ms)	715 (144)	662 (246)	674 (167)
		Errors	.01	.02	.02

Note: RTs shown as mean (sd)

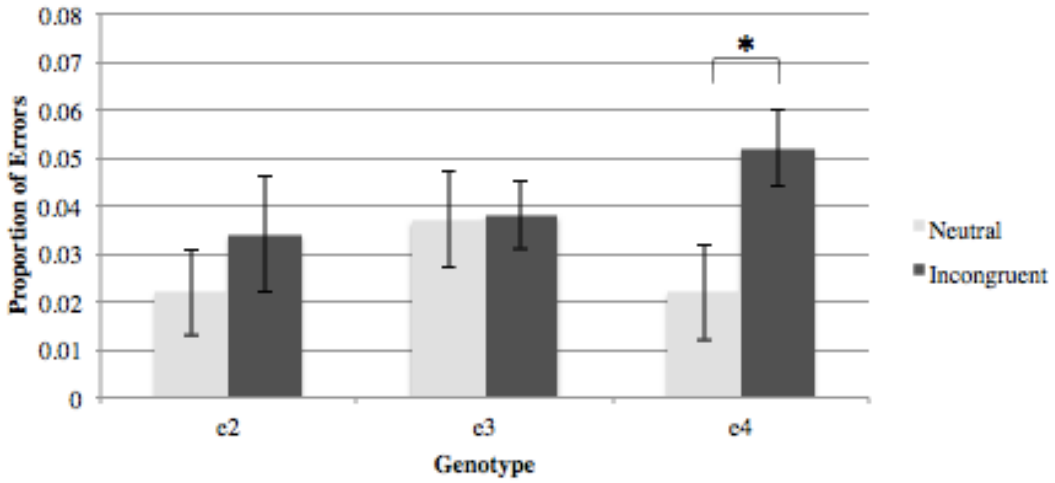

Figure 3. The proportion of errors made for congruent and incongruent stimuli shown by genotype group.

4. Discussion

The aim of current study was to establish whether *APOE* genotype is associated with differences in attentional control in mid-adulthood. By including all three genotype groups, results provide a novel exploration into the opposing effects of *APOE* status on cognitive ageing.

The current findings suggest deficits in attentional control are detectable by mid-adulthood in e4 carriers, however, effects were not uniform across cognitive measures. Carriers of this allele demonstrated a larger effect of incongruency on errors during a computerized Stroop-switch task. Similarly, there was a trend for e4 carriers to show reduced accuracy of PM retrieval in comparison to the population norm (e3 homozygotes). Despite the expectation

that e2 carriers would show cognitive advantages in mid-adulthood, in line with the suggested protective effects of this allele, results did not consistently support performance advantages. On the RVIP measure of sustained attention, compared to both homozygous e3 carriers and the e4 group, e2 carriers detected fewer target strings. On the control deck of the PM task e2 carriers trended to sort cards with slower RTs. These differences were found despite there being no genotype differences in simple RTs, suggesting differences specifically relate to decision-making RT.

The study administered versions of the RVIP and card-sort PM tasks comparable to those previously reported to show a speed-accuracy trade-off in mid-age e4 carriers (Evans et al, 2014). Our results did not replicate this pattern, and this is unlikely to be a factor of the subtle differences in paradigms used. Although the Evans study used a 6-minute version of the task, the reported genotype differences were observed in the first 3 minutes, so this should have been replicable in the 4-minute version. Across these tasks, with the exception of PM retrieval, e4 carriers showed equivalent performance to the e3 group. This could be interpreted as e4 carriers having relatively sustained cognitive performance in mid-adulthood. This over-arching pattern is not inconsistent with the antagonistic pleiotropy hypothesis (Han & Bondi, 2008), that the e4 variant transitions from having advantageous to disadvantageous consequences in mid-adulthood.

Importantly, e4 carriers did show subtle deficits within select processes, prominently a marked congruency effect in the number of errors made on the Stroop task. Similarly, a marked increase in errors for incongruent trials was found to both predict and characterize AD (Balota et al., 2010; Hutchison et al., 2010). These parallel results indicate that performance on this task is an important early identifier of cognitive decline, with the task showing sensitivity by mid-adulthood. Although previous research has reported no effect of *APOE* e4 on Stroop-task performance in mid-age (Sager et al., 2005; Trachtenberg, Filippini, Cheeseman, et al., 2012), the paradigm used here collected data on a trial-by-trial basis, providing a more sensitive measure.

In terms of specific cognitive processes, the computerized Stroop task requires both goal maintenance and response inhibition. Previous research suggests that RT distributions on this task are linked to detriments in inhibitory control, whereas errors represent failures to maintain task goals (Kane & Engle, 2003). Accordingly, e4 carriers showed decrements in the executive attention required for active goal maintenance. Notably, they also showed deficits in PM retrieval, in which both active maintenance of the PM intention, and monitoring of the environment for the opportunity to act are required, consistent with detriments in sustaining information at the forefront of attention.

Attentional control, as indexed by Stroop errors and PM performance, has been linked to WM span (Kane & Engle, 2003). Likewise, active updating and monitoring, the component of EF most closely assessed by the three paradigms administered in the current study, is described as being closely associated with WM (Miyake et al., 2000). In this study however, no genotype difference was found on a backward digit-span measure. It may be that future study, including a more detailed exploration of WM ability, would demonstrate sensitivity to *APOE* effects in mid-adulthood, for example the Operation Span task (Turner & Engle, 1989). In a slightly older sample (50-79 years), e4 carriers showed deficits on this task (Rosen et al.,

2002). An important avenue for future research is establishing a reproducible effect of *APOE* e4 genotype on the active processing of information in attention, and the neural basis of this difference.

Results from previous fMRI research suggest reported correlations between advantaged PM retrieval in e4 carriers and heightened inferior frontal gyrus activity might represent an early compensatory frontal shift (Evans et al., 2014). As activity of the inferior frontal gyrus has previously been associated with detection of salient stimuli (Hampshire et al., 2010), increased activity in this area fits with heightened PM accuracy. No evidence was provided in this study for e4 carriers showing any advantages in performance measures, however.

An important avenue for future research is to establish the mechanisms behind the *APOE* e4 effects on attentional control. *APOE* e4 is known to influence the profile of amyloid deposition in the brain (Morris et al., 2010; Villemagne et al., 2011). The detrimental effect of *APOE* e4 on executive attention in older adulthood and the very early stages of AD is likely mediated in part by amyloid deposition in regions including the prefrontal cortex (Aschenbrenner et al., 2014). Research probing the relationship between *APOE* e4 and amyloid across the lifespan found that despite no episodic memory performance difference, e4 carriers showed accelerated deposition of amyloid, with 10% of the population defined as amyloid positive by halfway through the fifth decade (Jack et al., 2015). This may also be the route by which *APOE* e4 impacts functional connectivity (Sheline et al., 2010), demonstrated in the earlier research of Trachtenberg et al (2012a; 2012b). These changes may be particularly relevant for executive attention, which requires communication between multiple processing regions. Imaging techniques should be used to explore which neural mechanisms are most relevant for the initial stages of cognitive ageing in e4 carriers.

At present, there is insufficient research on the cognitive profile of healthy e2 carriers. The current results, however, contrast with past research suggesting e2 is protective (Chiang et al., 2010; Farrer et al., 1997; Helkala et al., 1996; Lippa et al., 1997; Wilson et al., 2002). The results reported here are based on a small sample of e2 carriers, but contribute to the small number of studies that have explored e2 effects on cognition prior to older-adulthood (Alexander et al., 2007; Alexopoulos et al., 2011). Recent papers have reported differential spatial navigation strategies in e2 carriers in youth (Konishi et al., 2016), as well as altered memory function in individuals diagnosed with post-traumatic stress disorder (Freeman et al., 2005; Johnson et al., 2015; Kim et al., 2013). Therefore, although it may be possible to detect e2 differences earlier in the lifespan, the link between *APOE* e2 and executive attention is also relatively unexplored.

Recent research, however, reported overlap in the functional activation patterns of e2 and e4 carriers compared to e3 carriers, despite no behavioural differences (Trachtenberg et al., 2012a; Trachtenberg et al., 2012b). Whereas, the behavioural profile of e2 carriers and e4 in the current study did not overlap, both groups showed some disadvantage in attentional control. This encourages a closer examination of the hypothesised polarity in *APOE* effects. Our behavioural results suggest late-life dementia risk might not equate with cognitive performance in mid-adulthood, with both e2 and e4 carriers showing process-specific detriments. It may be that e4 carriers show increased vulnerability to cognitive insult (Wirth et al., 2014), whereas e2 carriers are better able to employ protective mechanisms. In support

of a compensatory mechanism in e2 carriers, in adults aged 90+ years, carriers of this variant were significantly less likely to meet clinical criteria for AD diagnoses, despite similar levels of AD neuropathology between e2 and e4 genotypes at autopsy (Berlau et al, 2009). Reports have also been made, however, that e2 is protective against amyloid deposition in later life (Morris et al., 2010), and in AD (Nagy et al., 1995).

Several limitations of the current study must be acknowledged. First, the number of participants within each genotype group was relatively small, meaning analysis may have lacked statistical power. This also limited exploration of gene dose effects. Effects of e4 gene dose (i.e. increased impact with 0, 1, and 2 e4 alleles) have been reported (Farrer et al., 1997; Raber et al., 2004; Wilson et al, 2011), however, the effects of e2 zygosity are less clearly demonstrated (Farrer et al., 1997). An additional analysis to the results reported here found no differences by *APOE* haplotype, but this would need to be further determined in future research. In addition, performance on the PM task was close to ceiling, and so the task may have lacked sensitivity for discriminating between genotype groups. Future research would benefit from increasing the demands placed on the attentional control system, for example by increasing the resource needs of the ongoing task.

4.1 Conclusions

In this study, both those carrying detrimental and protective variants of *APOE* showed decrements in executive attention by mid-adulthood. In e4 carriers, subtle disadvantages on a Stroop task and in PM retrieval were apparent, suggestive of deficits in goal-maintenance in the face of irrelevant information processing. This indicates that through the application of sensitive research paradigms, it is possible to identify those at genetic risk of cognitive decline from mid-adulthood. Surprisingly, behavioural disadvantages were identified in e2 carriers, despite the premised benefits of carrying this allele for cognitive health in older adulthood. Of critical importance, results illustrate the importance of including e2 carriers as an independent group, and the need to establish both how this variant influences cognition and neural function across the lifespan, and how it interacts with environmental factors to promote protection against age-related cognitive decline.

Conflicts of interest: none

Acknowledgements

This study was funded by an Economic and Social Research Council studentship and the Sussex Partnership NHS Foundation Trust.

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